Oxitec's GE Mosquito Experimental Use Permit OX5034

Status: Oxitec's response to 10-day deficiency letter received (July 16, 2019); response in review.

Previous Application

- Oxitec had applied for an EUP for a different GE mosquito, OX513A *Aedes aegypti*, but withdrew prior to EPA's completion of a full risk assessment.
- These OX513A male mosquitoes if released and mated with wild female mosquitoes, have no surviving offspring due to the GE introduced protein tTAV (tetracycline transactivator variant).

EUP Background

- Oxitec currently has another EUP application in for a 2nd Generation GE mosquito, OX5034 *Aedes aegypti,* which also contain tTAV but work somewhat differently. Like OX513A, the new OX5034 also contains the marker DsRed2 protein which turns red under UV light.
- Request for OX5034 EUP is for 2 years to assess efficacy in US.
- Proposed GE mosquito releases on 5,000 acres in Harris County, Texas and Monroe County, Florida.
- Final PRIA due date – November 1, 2019

Product Overview – How it Works

- In OX5034 *Aedes aegypti* mosquitoes the tTAV protein only accumulates and kills juvenile female mosquitoes; in OX5034, tTAV is processed differently in males so that male mosquitoes survive.
- OX5034 GE male *Ae. aegypti* mosquitoes with the tTAV trait are released into the environment to mate with wild female *Ae. aegypti* mosquitoes.
- All female offspring from matings of GE male mosquitoes with wild female mosquitoes die. All male offspring from matings of GE male mosquitoes with wild female mosquitoes survive, and half of those offspring contain the trait for tTAV and can pass it on to subsequent generations.

Uncertainties and Risk Concerns for 5,000 Acre EUP Field Release

- **Human Health Risk – Allergencity to DsRed2 Not Yet Resolved**
  - During OPP's technical screen for the previous application (OX513A *Ae. aegypti*), DsRed2 was found to be substantially similar to "Akane", a protein from coral listed as an allergen in the allergenicity databases AllergenOnline and Compare.
  - In response to requests from Oxitec, the panels for both AllergenOnline and Compare reevaluated the research publication on Akane and subsequently removed it from their databases.
  - Both panels independently agreed that the researchers failed to provide enough evidence to demonstrate that Akane was the cause of the allergic reactions.
  - For OPP, removal of Akane from the two databases does not resolve the potential risk of DsRed2 allergenicity. OPP needs additional data to make this determination. As our review is pending, these data have not yet been communicated. However, they may not be needed for the EUP release if no exposure can be confirmed.

- **Human Health Risk – No exposure not yet confirmed.**
  - Insufficient data were originally submitted with the OX5034 application to confirm that OX5034 GE female mosquitoes will not be released or found in subsequent generations and be able to bite people.
  - Penetrance data requested in the 10-day letter to confirm no exposure.
  - **Importance:** These data are necessary to confirm no GE mosquitoes will bite people.

- **Experimental Program - Information on experimental design to confirm maximum acreage and application rate for testing.**
  - Insufficient experimental design information, identifying the number of treatments and replicates that will be tested, were originally submitted with the OX5034 application.
  - **Importance:** This information is necessary to identify the acreage to be tested for the FR Notice of Receipt and for the EUP issuance letter.

Additional Uncertainty for Commercial Use that Could be Evaluated During the EUP Field Releases

- No characterization of non-GE traits in the lab strain used to make the GE OX5034 mosquitoes.
  - These non-GE traits could integrate into wild mosquito populations because OX5034 males survive.
  - Additional information needed for commercial use to ensure that undesirable traits (e.g., genetic trait for increased egg laying) which might increase the risk associated with modified mosquitoes do not integrate into wild mosquito populations.
  - **Importance:** Information is necessary to make ecological and human health safety findings for commercial registration.

Public Comments Received for Oxitec's 1st EUP Application, OX513A, Highlight Concerns Listed Above

- Also of concern is that biting female GE mosquitoes may inject a novel engineered protein into humans; Oxitec has yet to conduct or publish any study showing that this novel protein is not expressed in the mosquito's salivary gland." [Friends of the Earth p. 4]
- "…Research should establish that any escaped GE females would not be more effective transmitters of viruses like dengue and zika." [Center for Food Safety 0356 p. 20]
- "When Oxitec's GE mosquitoes breed with wild mosquitoes some of their other genetic characteristics will be passed on to the local wild mosquito population. Different strains of the same species are found in different places and some strains are more resistant to insecticides than others or better transmitters of disease […] *Aedes aegypti* may transmit zika, chikungunya, yellow fever and four different serotypes of dengue, yet strains may vary significantly in their ability to transmit these tropical diseases.[70-77] […] The possible introduction of such traits needs to be considered." [GeneWatch 0085 p. 8]
- "EPA should prepare a full evaluation the potential allergenicity that could be caused by a GE *Aedes aegypti* mosquito bite. […] However, the company did not do any human trials to examine whether this is demonstrated in actual bites on humans. The (*FDA*) EA failed to analyze the potential allergenicity caused by a GE mosquito bite by relying on unproven assumptions." [Center for Food Safety 0356 p. 12]